SAHA Patient: IV vs ORAL (200 mg/dose)

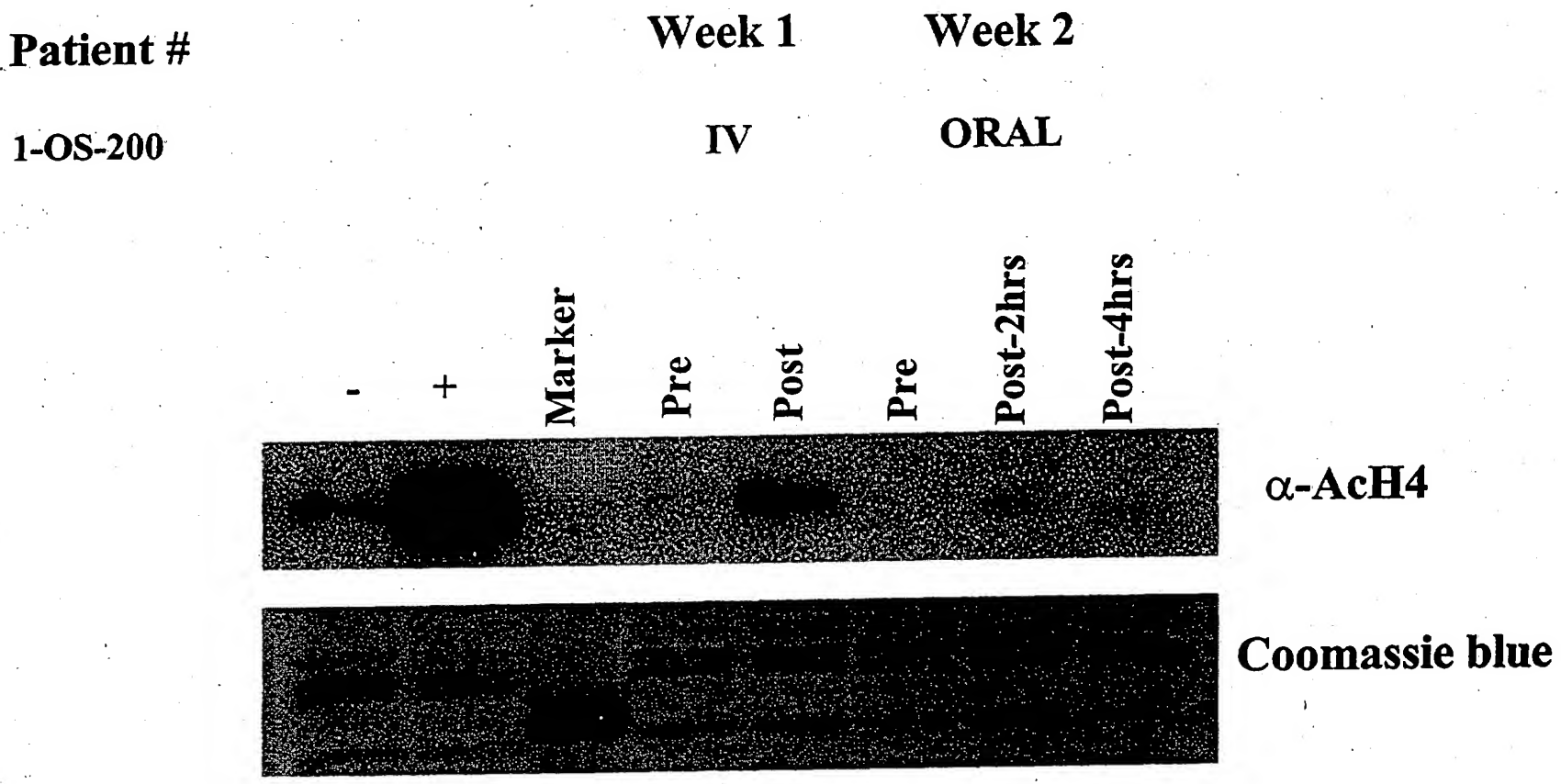


FIG. 1

Protocol 01-021 (ORAL SAHA) ARM A: SOLID TUMOR PATIENTS Cohort I (200 mg/dose)

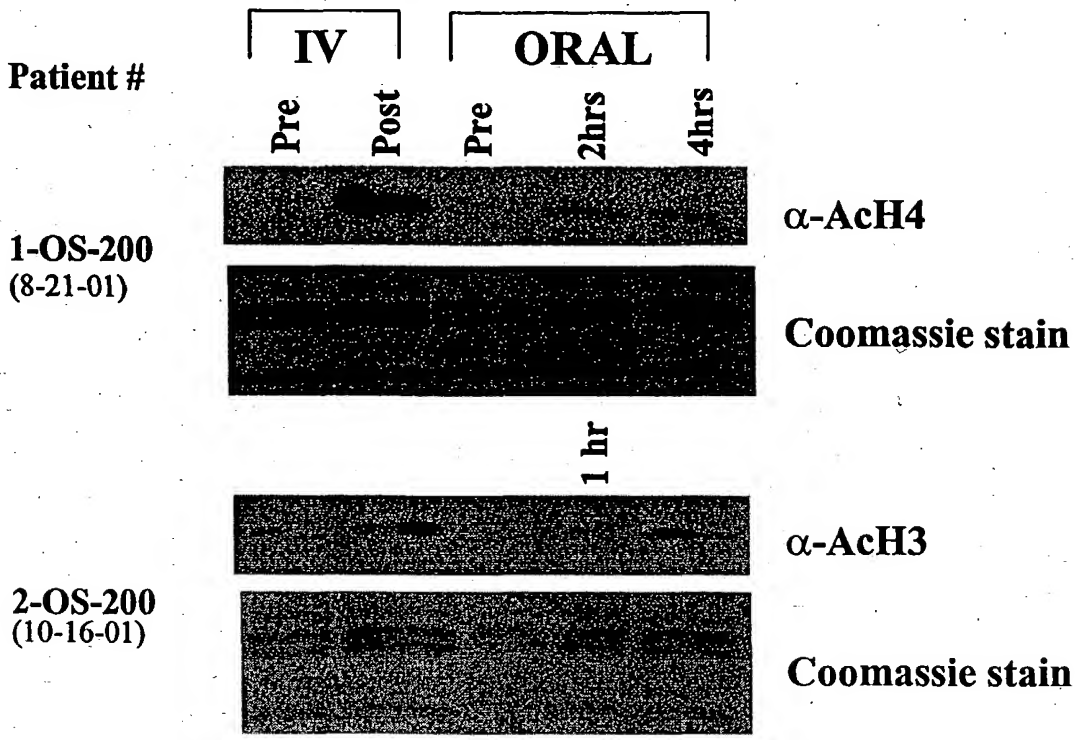


FIG. 2

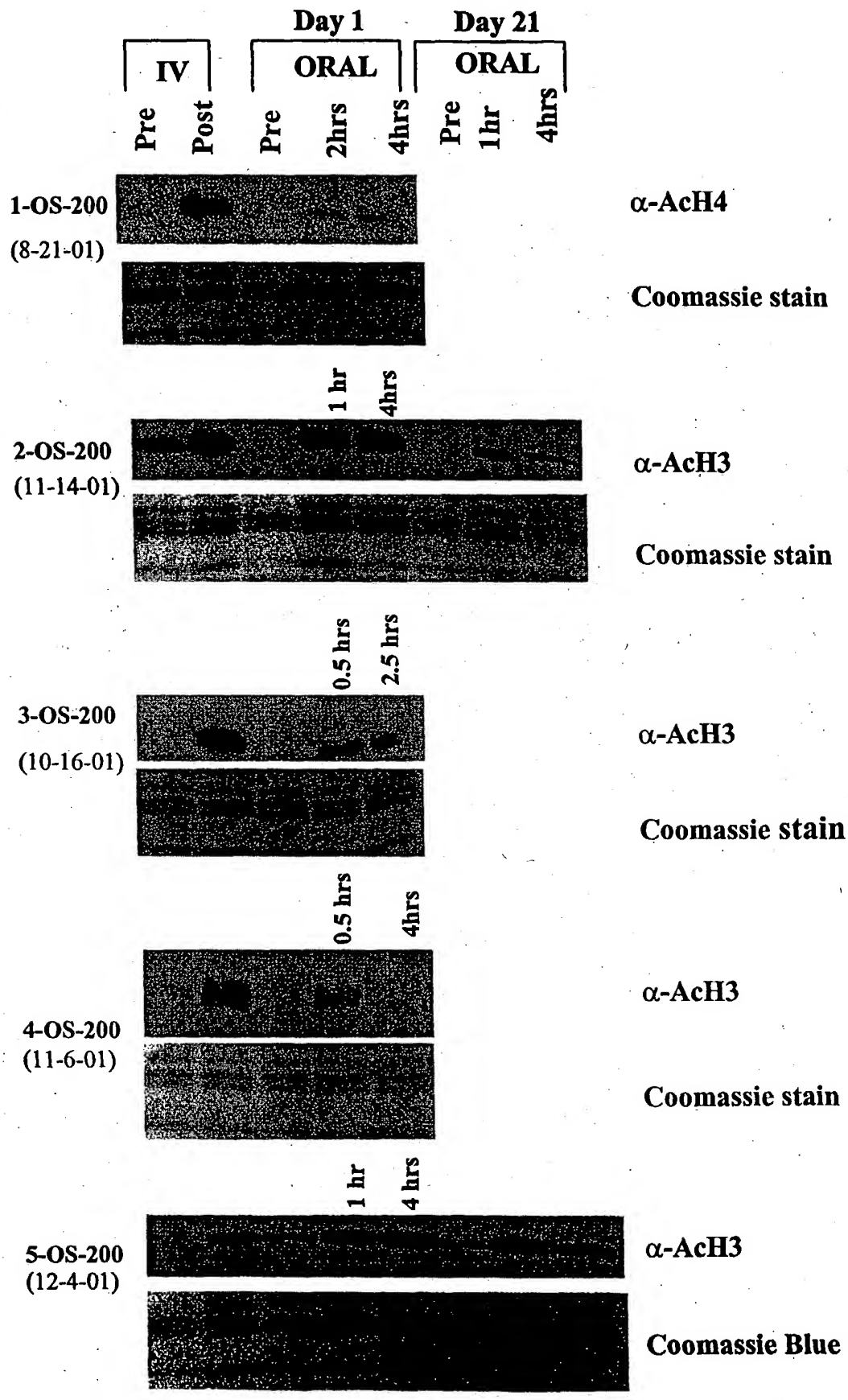
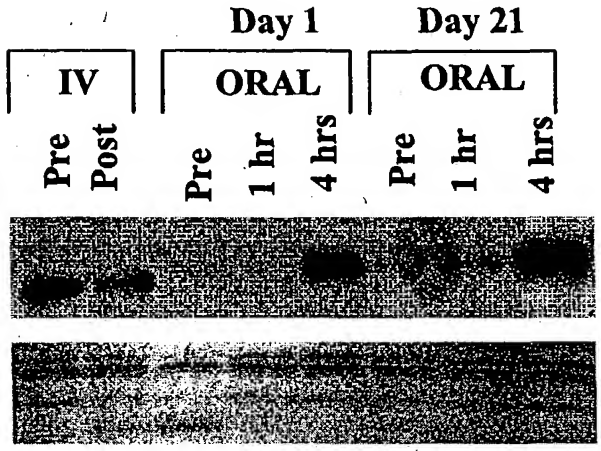

SAHA Patients: ORAL /Cohort I (200 mg/dose)
Day 1
Day 21
IV
ORAL
ORAL
Pre
Post
Pre
2hrs
4hrs
Pre
1hr
4hrs
1-OS-200
(8-21-01)
α-AcH4
Coomassie stain
1 hr
4hrs
2-OS-200
(11-14-01)
α-AcH3
Coomassie stain
0.5 hrs
2.5 hrs
3-OS-200
(10-16-01)
α-AcH3
Coomassie stain
0.5 hrs
4hrs
4-OS-200
(11-6-01)
α-AcH3
Coomassie stain
1 hr
4 hrs
5-OS-200
(12-4-01)
α-AcH3
Coomassie Blue

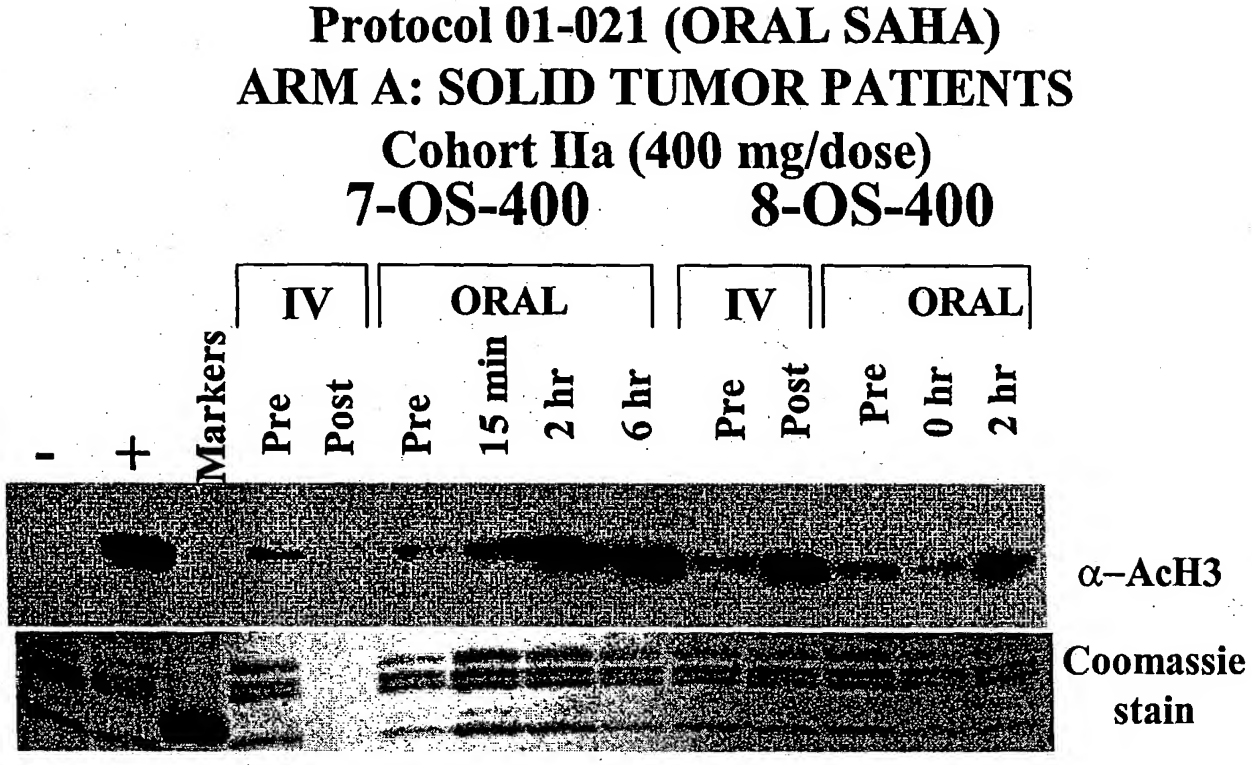
FIG. 3

Protocol 01-021 (ORAL SAHA)
ARM A: SOLID TUMOR PATIENTS
Cohort I (200 mg/dose)



6-OS-200
(12-13-01)

FIG. 4


Protocol 01-021 (ORAL SAHA)
ARM A: SOLID TUMOR PATIENTS
Cohort IIa (400 mg/dose)
7-OS-400
8-OS-400
IV
ORAL
IV
ORAL
-
+
Markers
Pre
Post
Pre
15 min
2 hr
6 hr
Pre
Post
Pre
0 hr
2 hr
α–AcH3
Coomassie stain
12/19/01

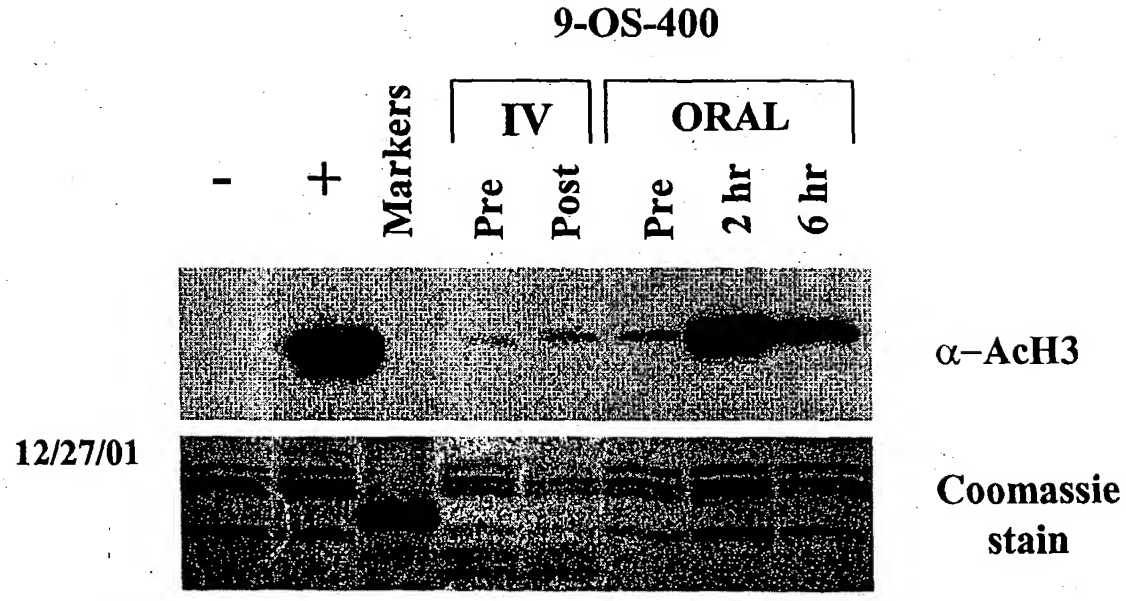

9-OS-400
IV
ORAL
-
+
Markers
Pre
Post
Pre
2 hr
6 hr
α–AcH3
12/27/01
Coomassie stain

FIG. 5

SAHA Patients: ORAL/Cohort II (400 mg/dose)

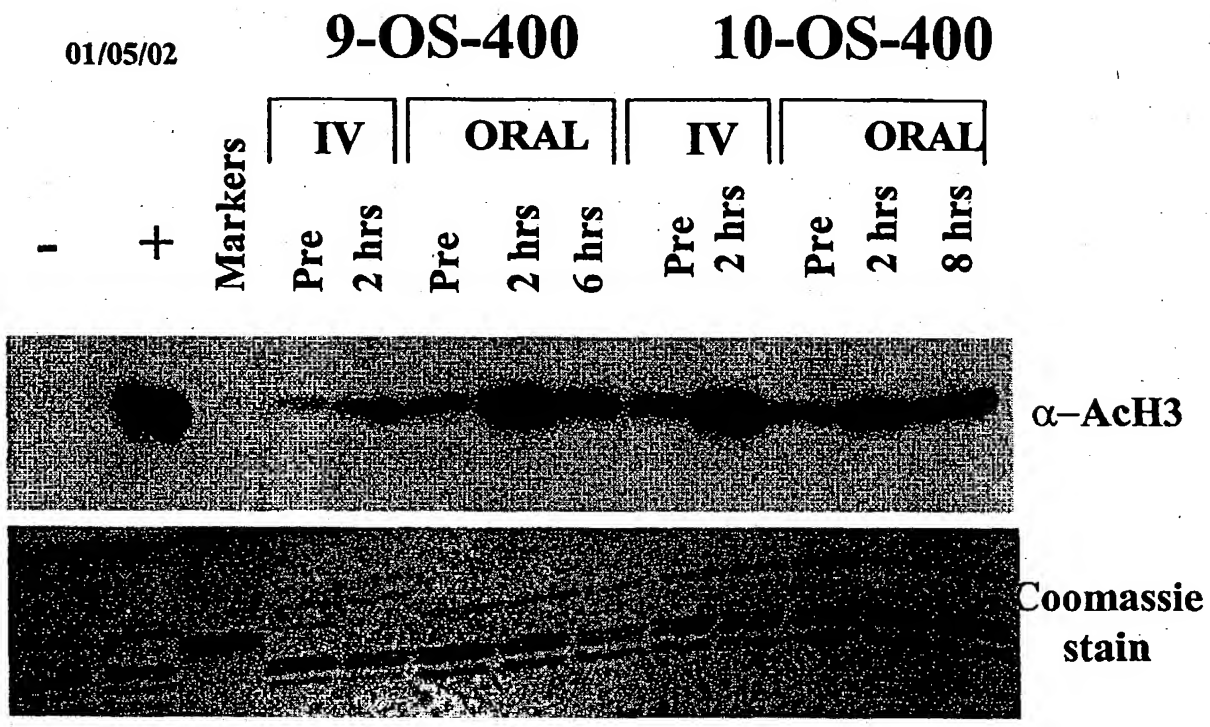


FIG. 6

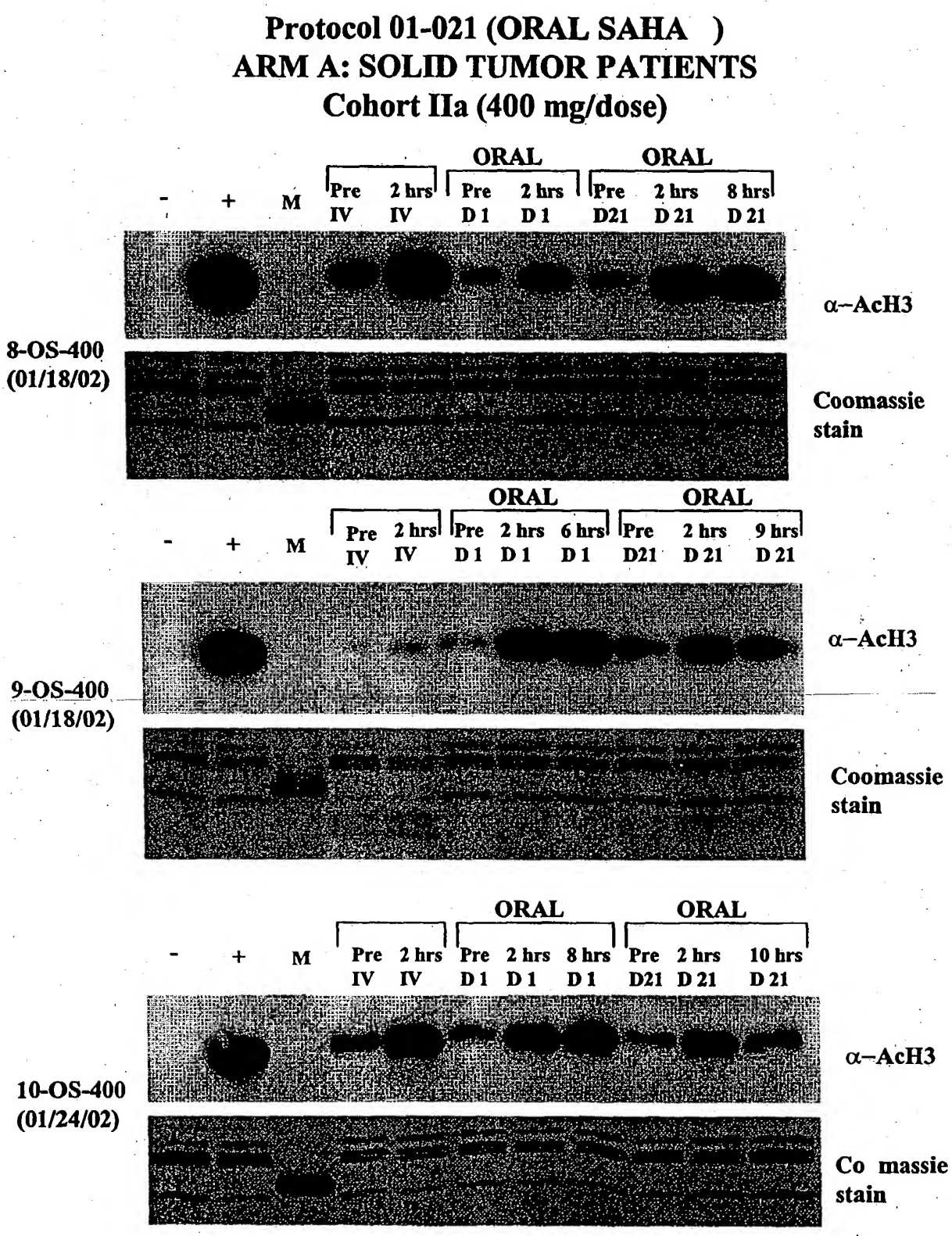
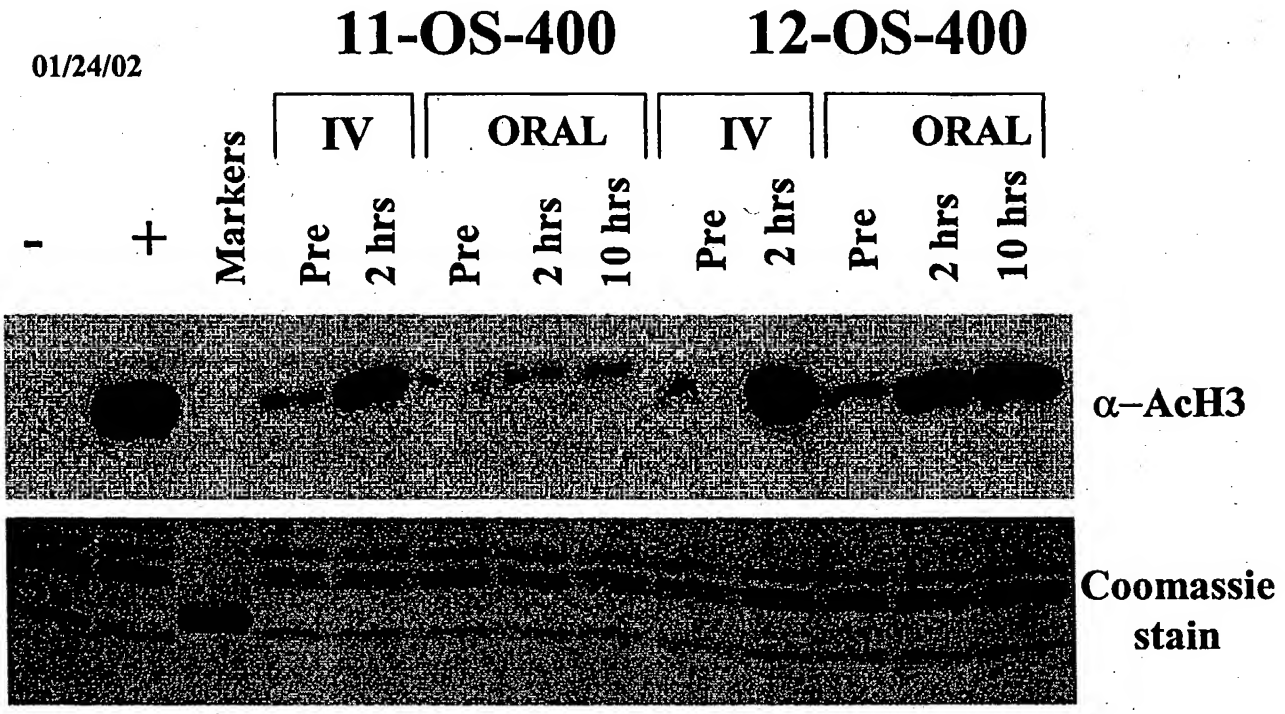

Protocol 01-021 (ORAL SAHA)
ARM A: SOLID TUMOR PATIENTS
Cohort IIa (400 mg/dose)
ORAL
ORAL
- + M
Pre IV
2 hrs IV
Pre D 1
2 hrs D 1
Pre D21
2 hrs D 21
8 hrs D 21
α–AcH3
8-OS-400 (01/18/02)
Coomassie stain
ORAL
ORAL
- + M
Pre IV
2 hrs IV
Pre D 1
2 hrs D 1
6 hrs D 1
Pre D21
2 hrs D 21
9 hrs D 21
α–AcH3
9-OS-400 (01/18/02)
Coomassie stain
ORAL
ORAL
- + M
Pre IV
2 hrs IV
Pre D 1
2 hrs D 1
8 hrs D 1
Pre D21
2 hrs D 21
10 hrs D 21
α–AcH3
10-OS-400 (01/24/02)
Co massie stain

FIG. 7

SAHA Patients: ORAL/Cohort II (400 mg/dose)



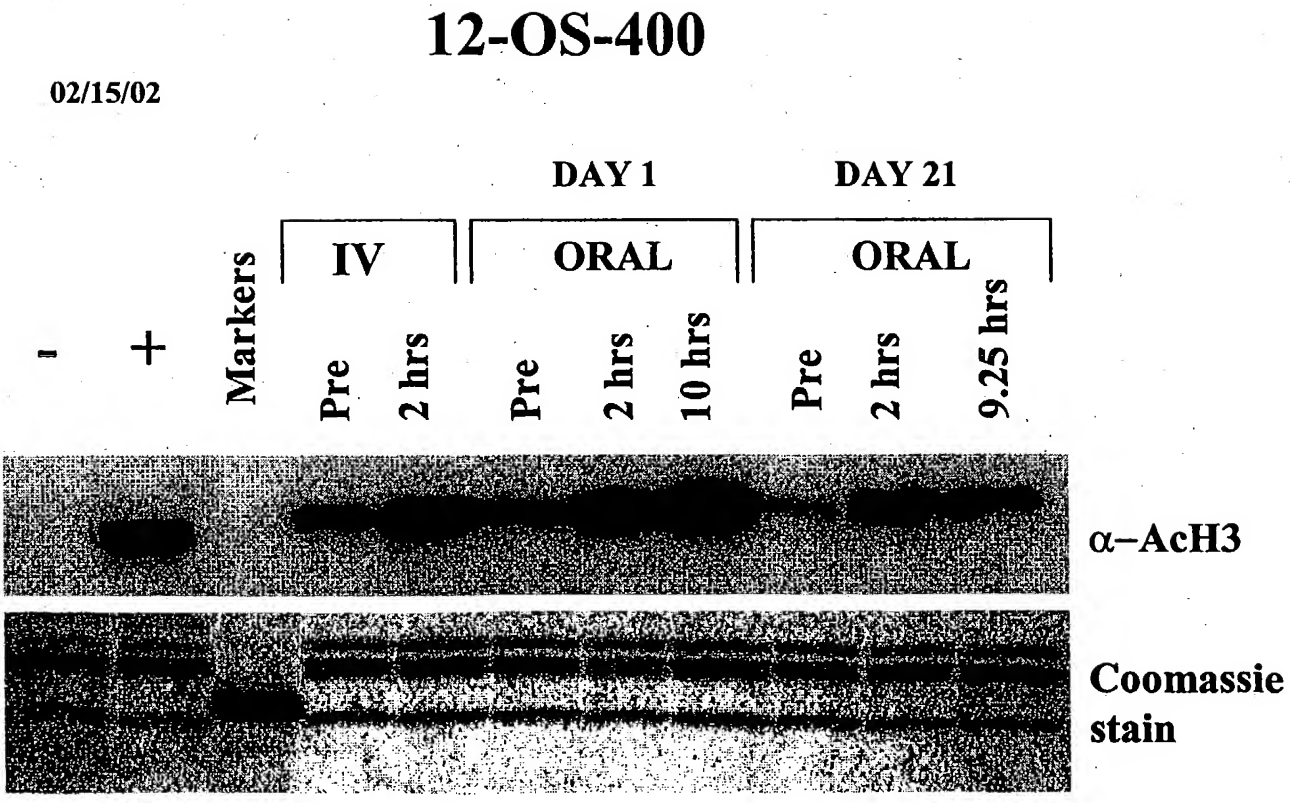


FIG. 8

Oral 200 mg vs. 400 mg (Fasting)

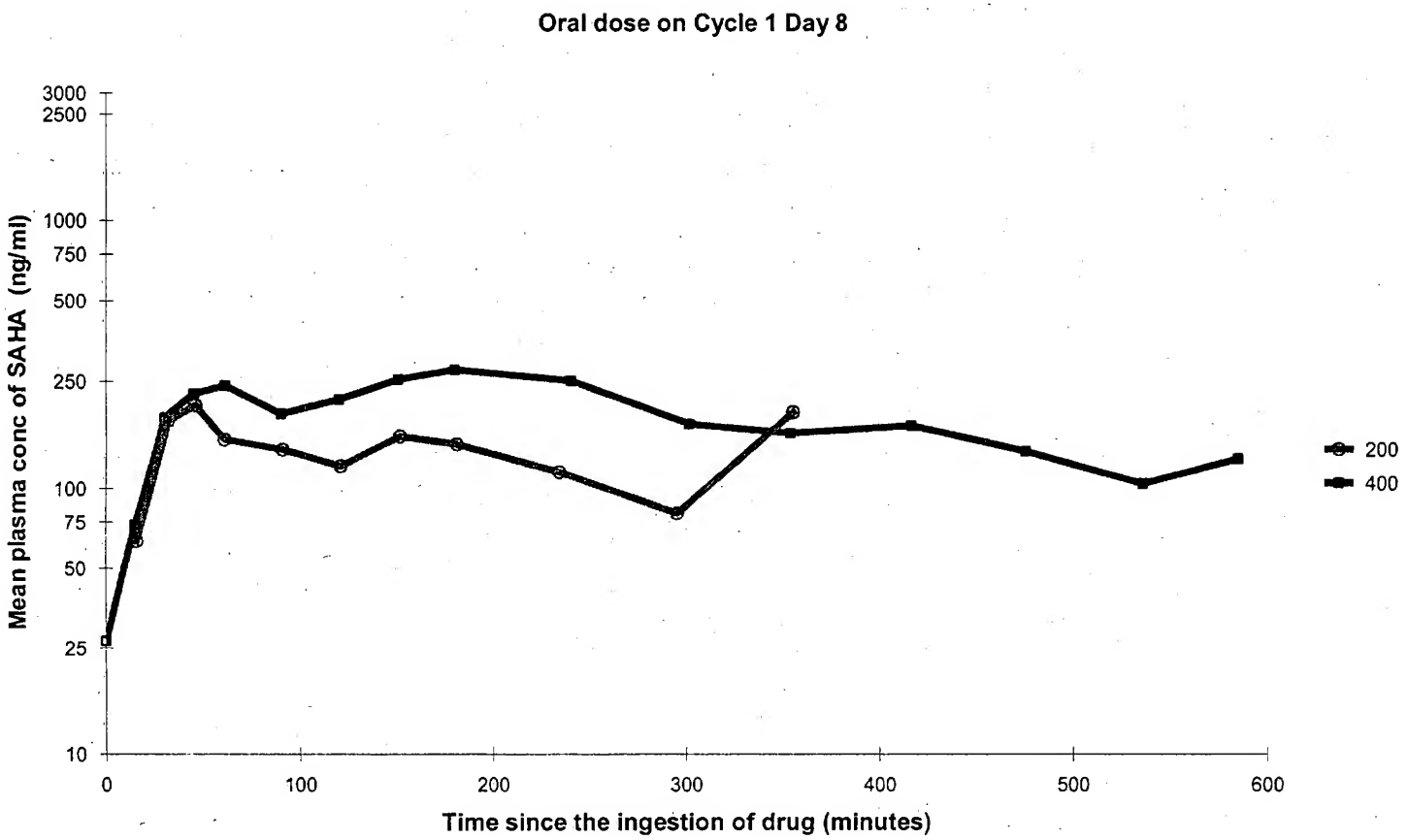


Figure 9A

Oral 200 mg vs. 400 mg (no-fasting)

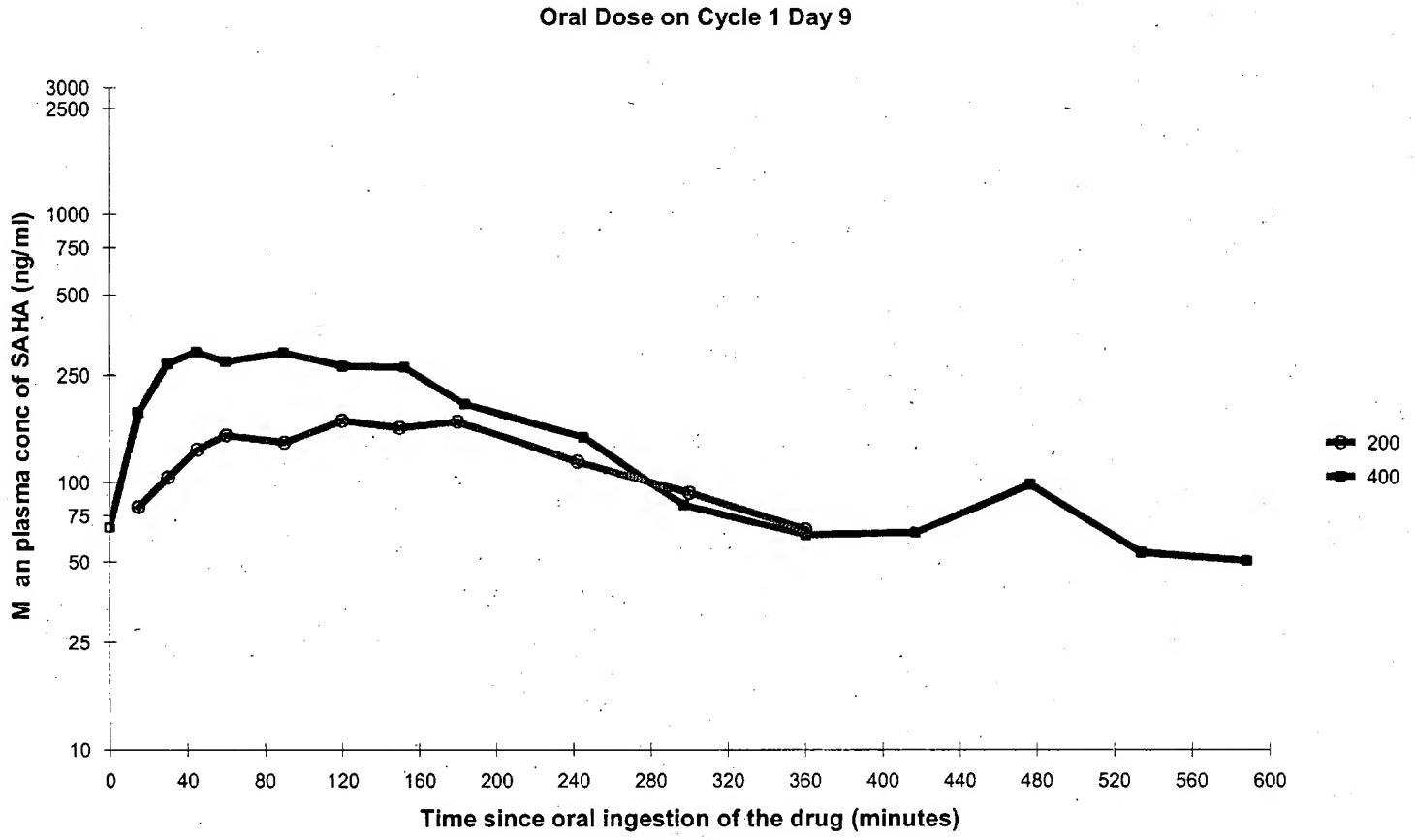


Figure 9B

IV 200 mg vs. 400 mg

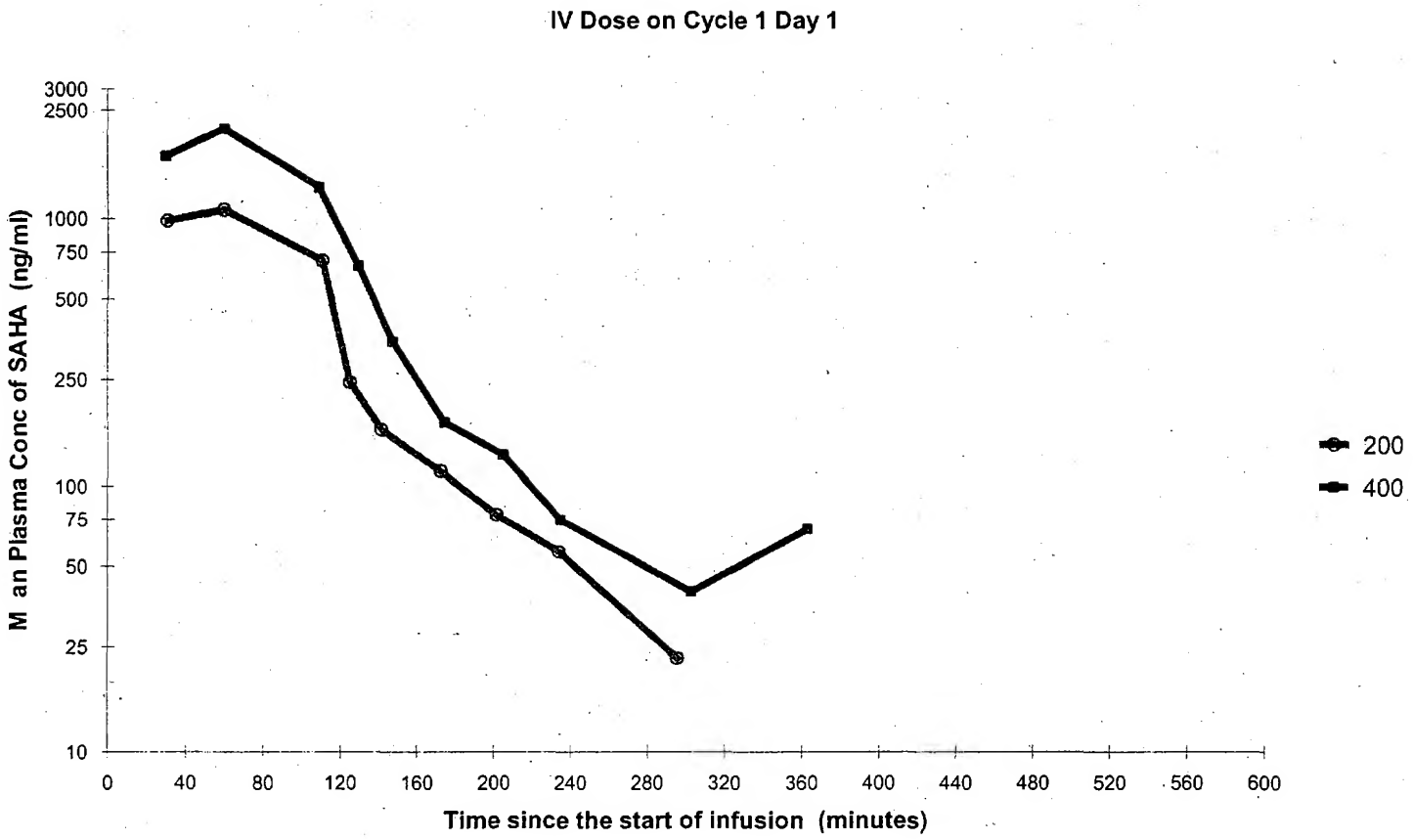
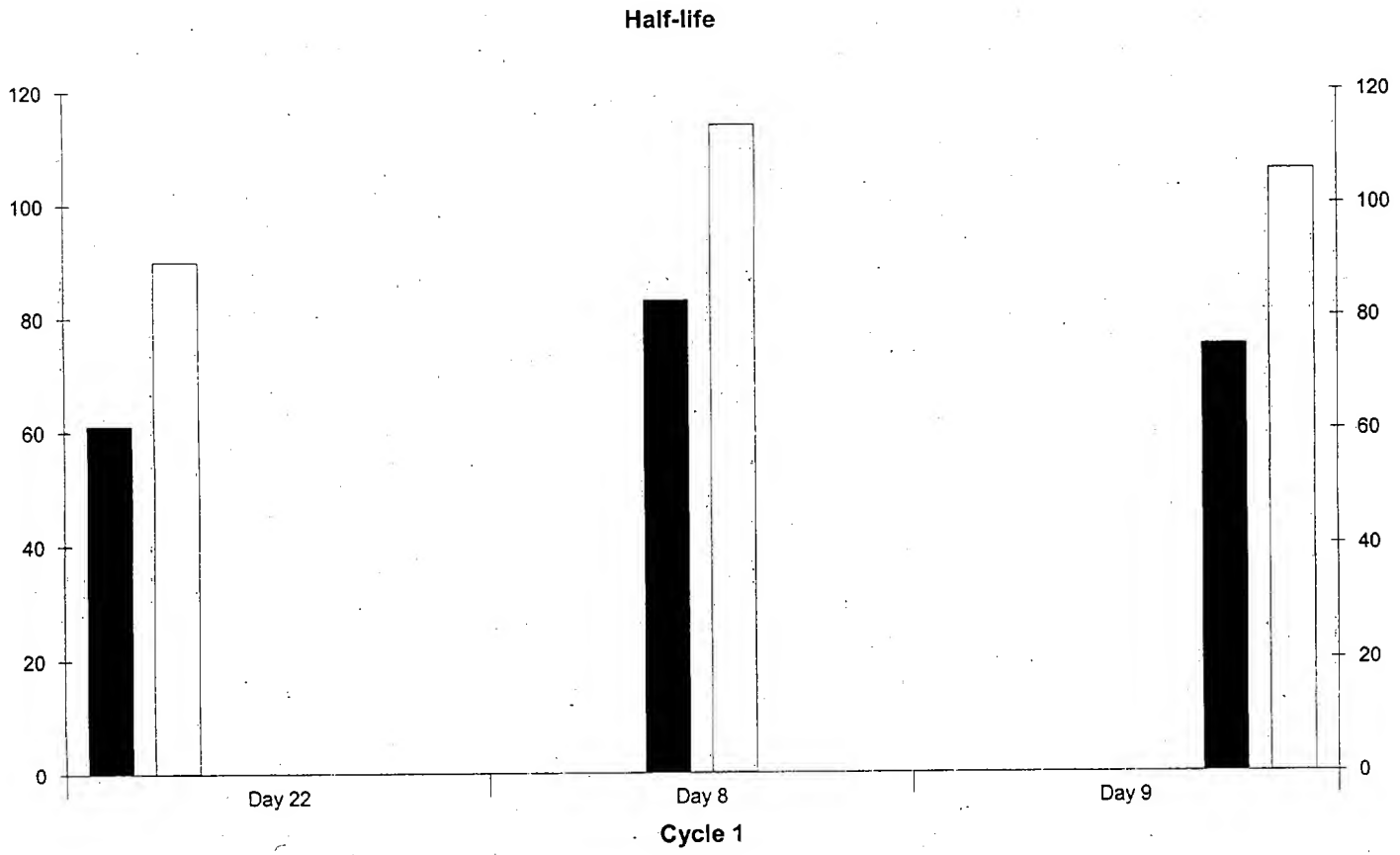


Figure 9C

Apparent Half-life of the Oral Dose

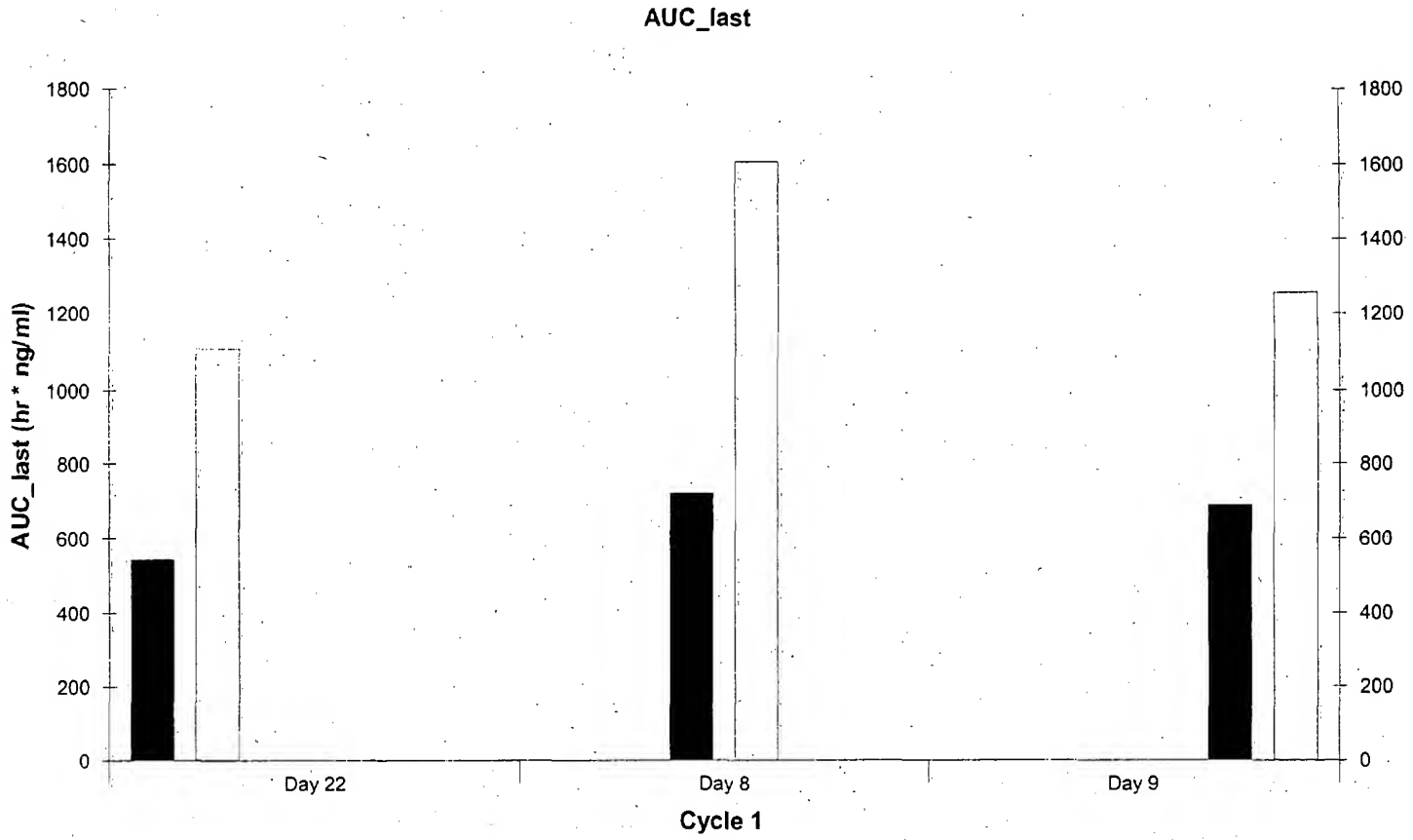


■=200 mg group (n=3-5); □=400 mg group (n=5-10)

3/4/2003

Figure 10

AUC of the Oral Dose

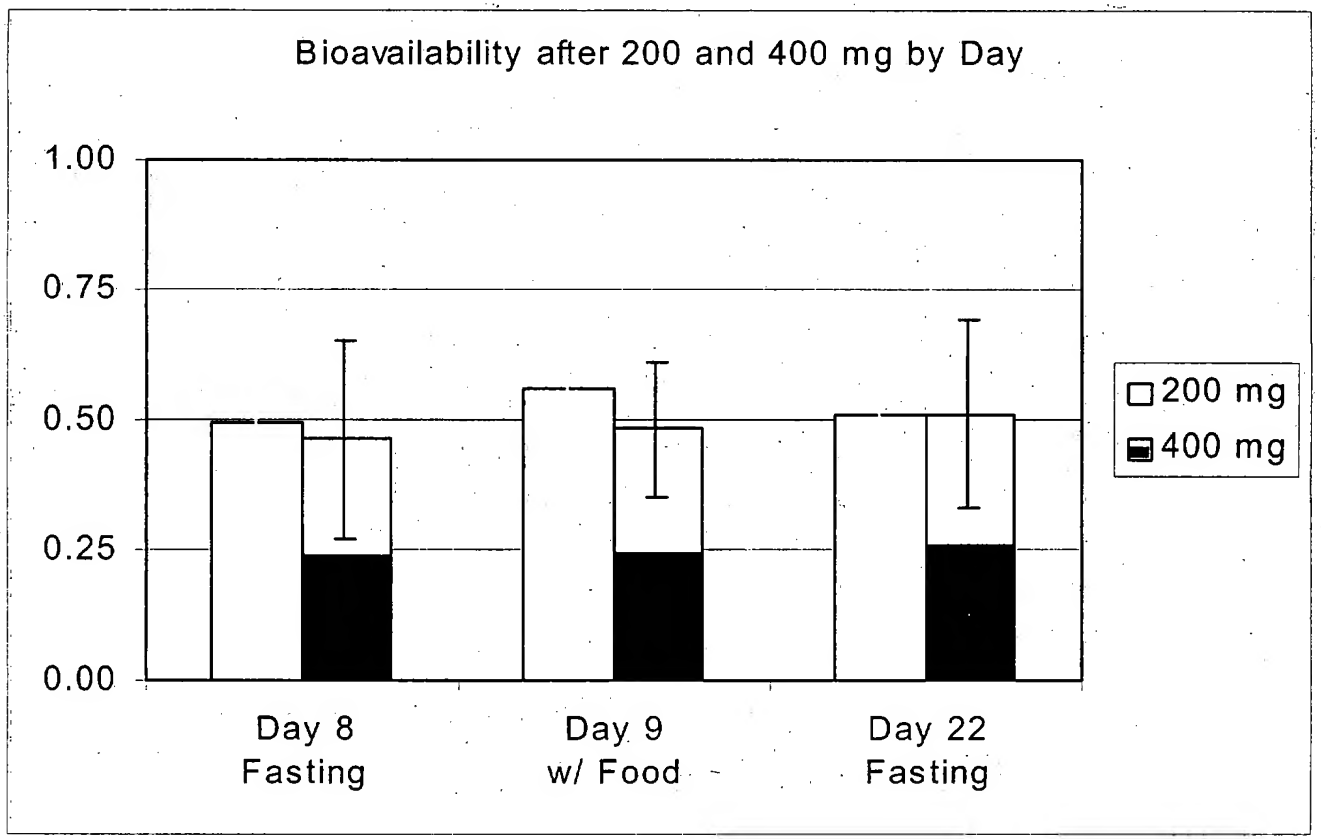


■ =200 mg group (n=3-5); □ =400 mg group (n=5-10)

3/4/2003

Figure 11

Bioavailability



F ~ 48%

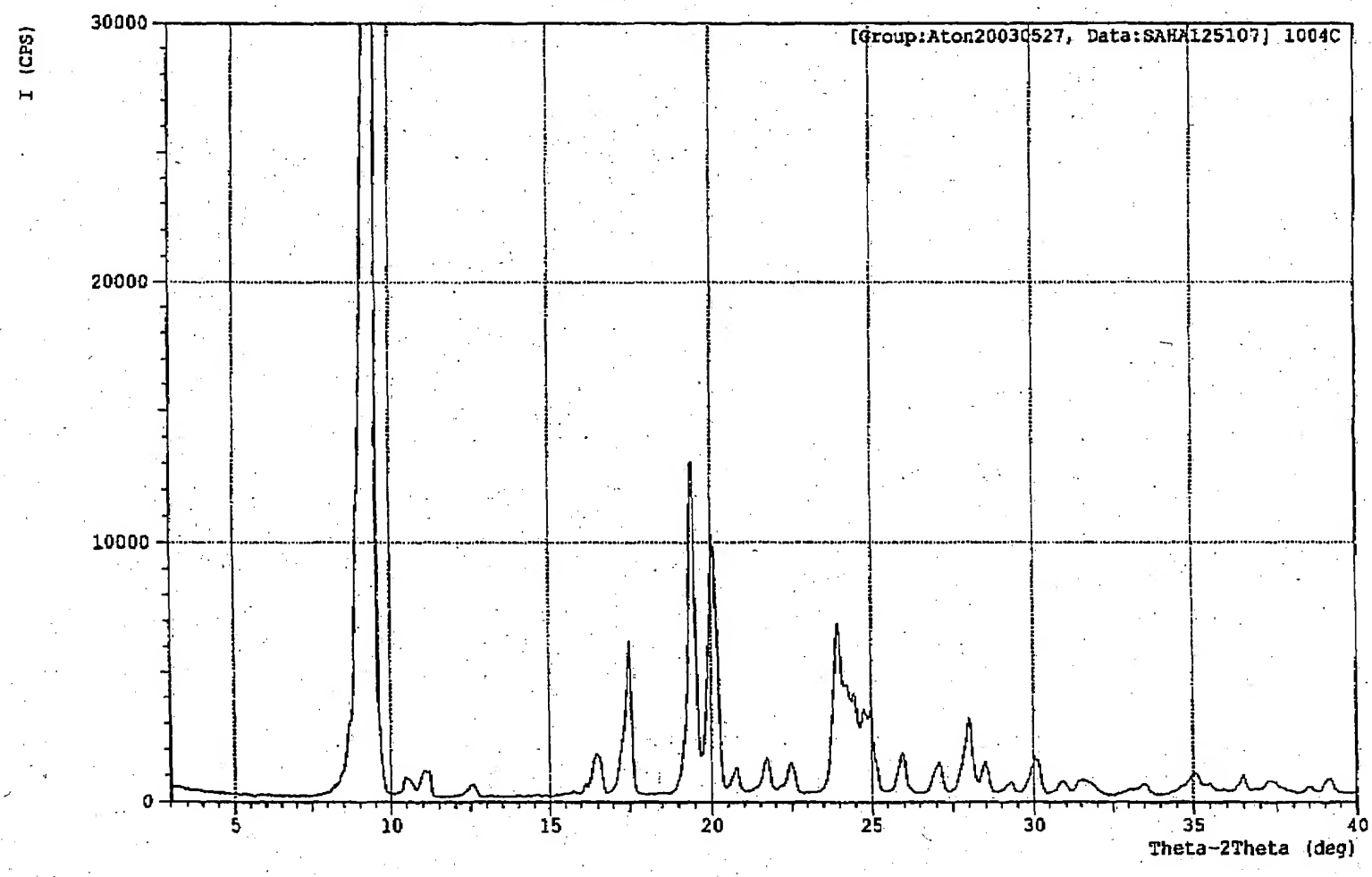
Figure 12

Fig 1BA
SAHA Gmp

*** Multi Plot ***

File Name : Aton20030527\SAHA125107
Sample Name : 1004C Comment : BJE-A-181 ARN # 02306
Date & Time : 05-27-03 12:29:34
Condition
X-ray Tube : Cu(1.54060 A) Voltage : 40.0 kV Current : 40.0 mA
Scan Range : 3.0000 <-> 45.0000 deg Step Size : 0.0400 deg
Count Time : 1.20 sec Slit DS : 1.00 deg SS : 1.00 deg RS : 0.30 mm

NAME BJE
DATE 5-27-03
NB # BJE-A-181



US'108 column

Fig 13B
Al US'108 column

NAME S Iyer
DATE 06/04/03
ID # SVI-A-157

A

*** Multi Plot ***

File Name : Aton20030606\SAHA123521
Sample Name : AP52-14-9-1 Comment : SVI-A-157
Date & Time : 06-06-03 12:13:51
Condition
X-ray Tube : Cu(1.54060 A) Voltage : 40.0 kV Current : 40.0 mA
Scan Range : 3.0000 <-> 45.0000 deg Step Size : 0.0400 deg
Count Time : 1.20 sec Slit DS : 1.00 deg SS : 1.00 deg RS : 0.30 mm

Al

New

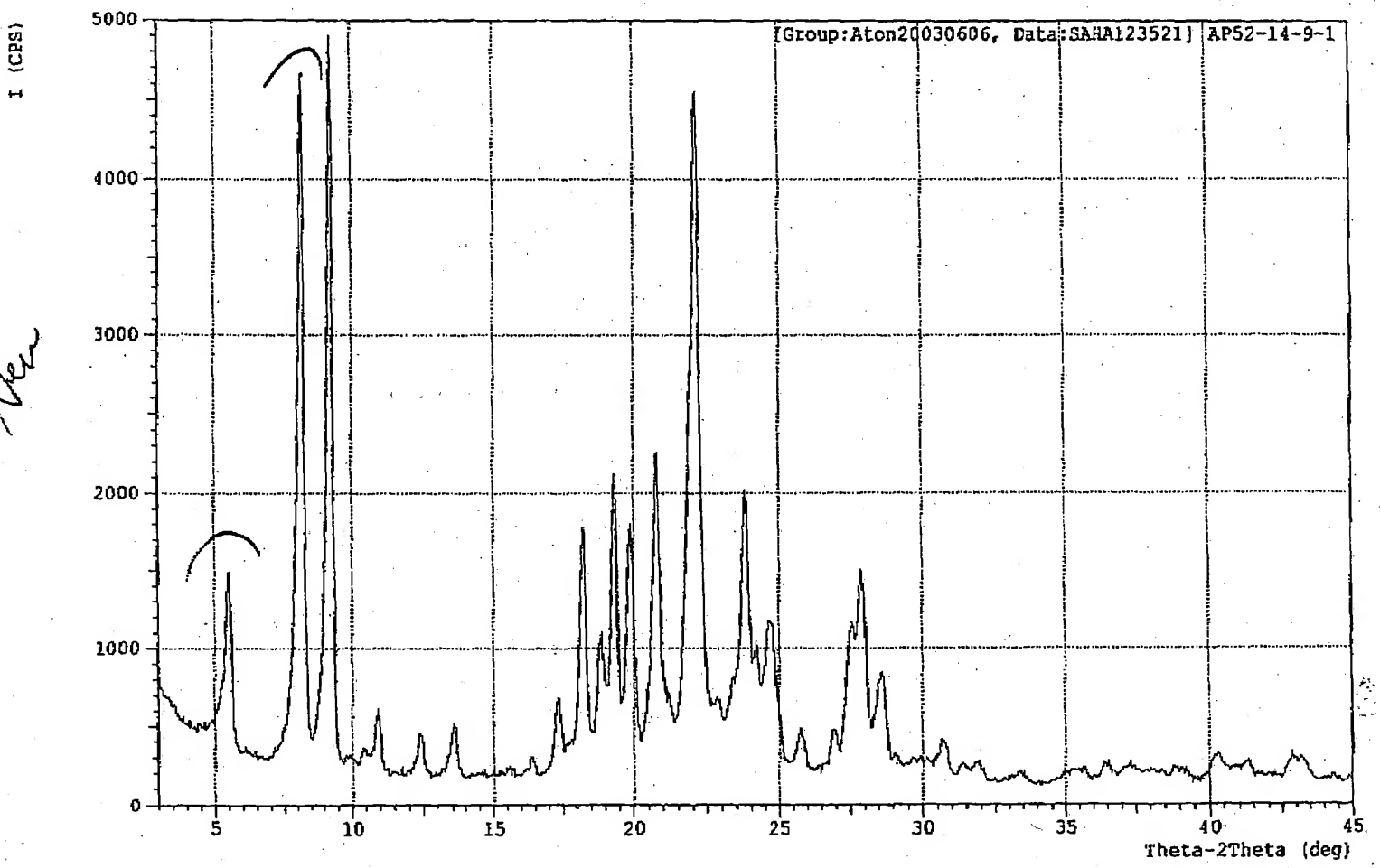


Fig 13C

US'108 Hydrogenation

*** Multi Plot ***

NAME S. Iyer
DATE 06/06/03
SVI-A-165

File Name : Aton20030606\SAHA145204
Sample Name : AP48-43-4 Comment : SVI-A-165
Date & Time : 06-06-03 14:30:32
Condition
X-ray Tube : Cu(1.54060 A) Voltage : 40.0 kV Current : 40.0 mA
Scan Range : 3.0000 <-> 45.0000 deg Step Size : 0.0400 deg
Count Time : 1.20 sec Slit DS : 1.00 deg SS : 1.00 deg RS : 0.30 mm

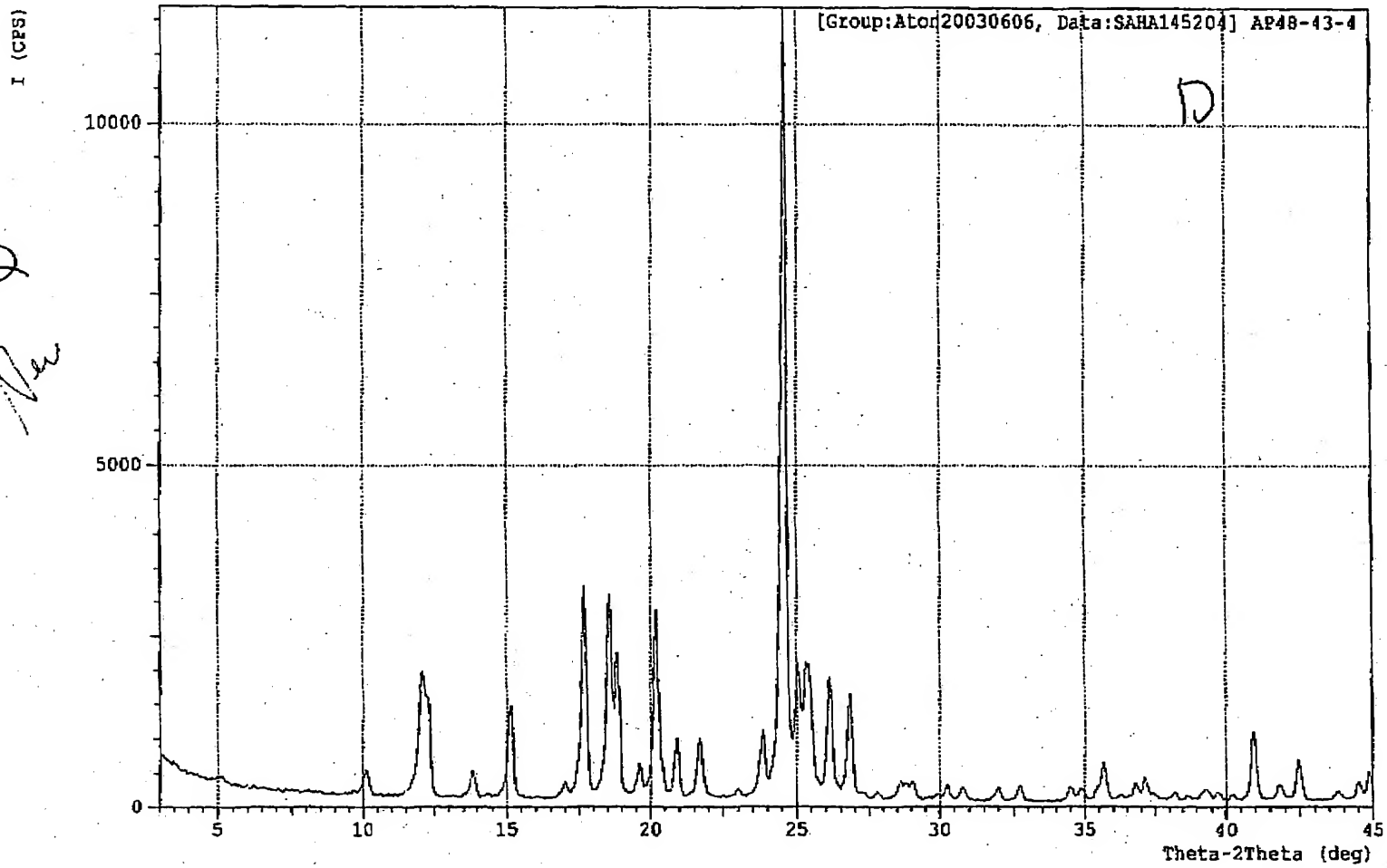


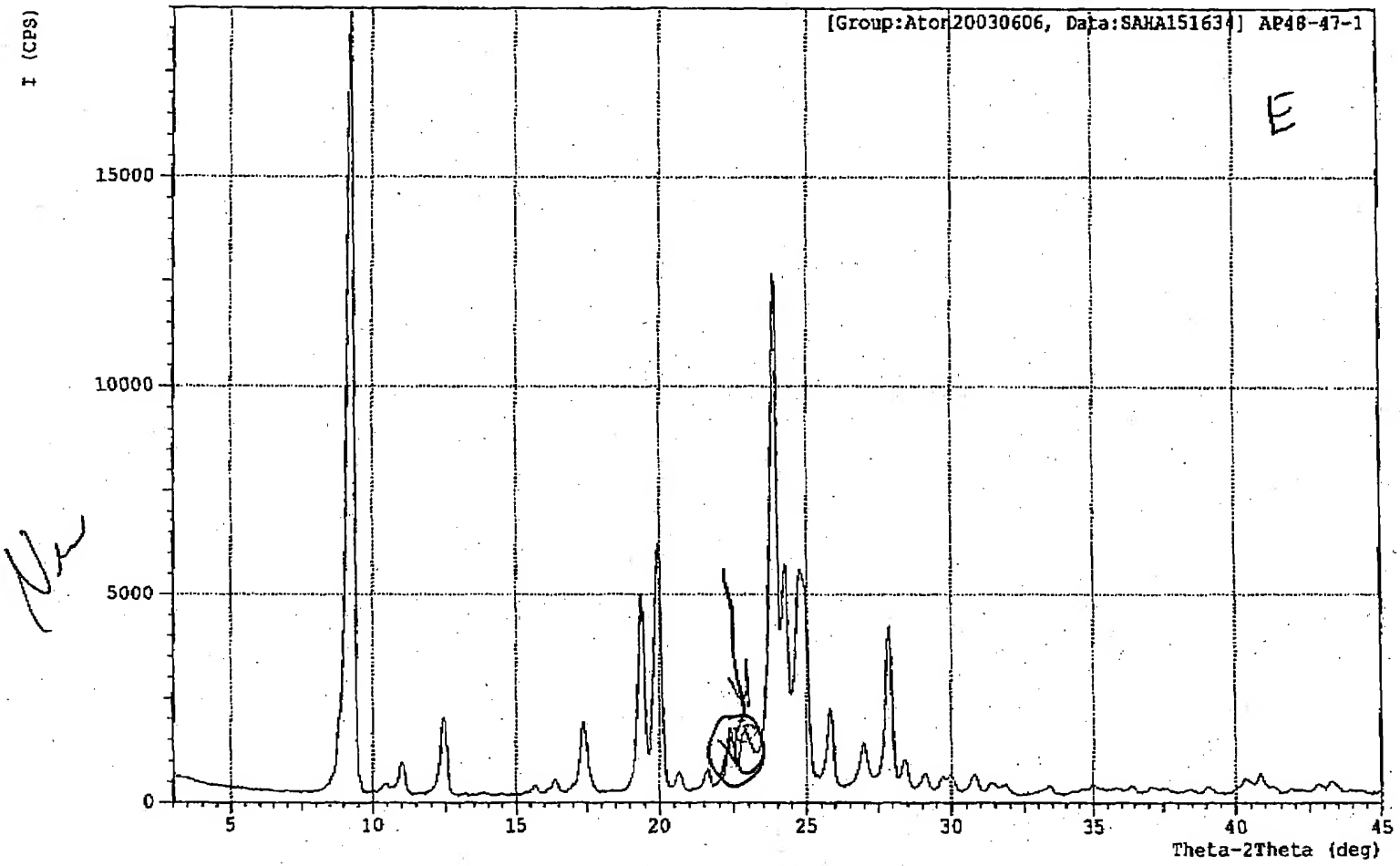
Fig 13D

CH_3CN

*** Multi Plot ***

NAME S Iyer
DATE 06/06/03
NB # SVI-A-167

File Name : Aton20030606\SAHA151634
Sample Name : AP48-47-1 Comment : SVI-A-167
Date & Time : 06-06-03 14:55:03
Condition
X-ray Tube : Cu(1.54060 A) Voltage : 40.0 kV Current : 40.0 mA
Scan Range : 3.0000 <-> 45.0000 deg Step Size : 0.0400 deg
Count Time : 1.20 sec Slit DS : 1.00 deg SS : 1.00 deg RS : 0.30 mm



E

CI

NH

↓ glacial acetic acid. (Stowell)

*** Multi Plot ***

Fig 3E

NAME S Iyer
DATE 06/06/03
SVI-A-161

File Name : Aton20030606\SAHA140222
Sample Name : AP52-18-10 Comment : SVI-A-161
Date & Time : 06-06-03 13:40:50
Condition
X-ray Tube : Cu(1.54060 A) Voltage : 40.0 kV Current : 40.0 mA
Scan Range : 3.0000 <-> 45.0000 deg Step Size : 0.0400 deg
Count Time : 1.20 sec Slit DS : 1.00 deg SS : 1.00 deg RS : 0.30 mm

G

D

New

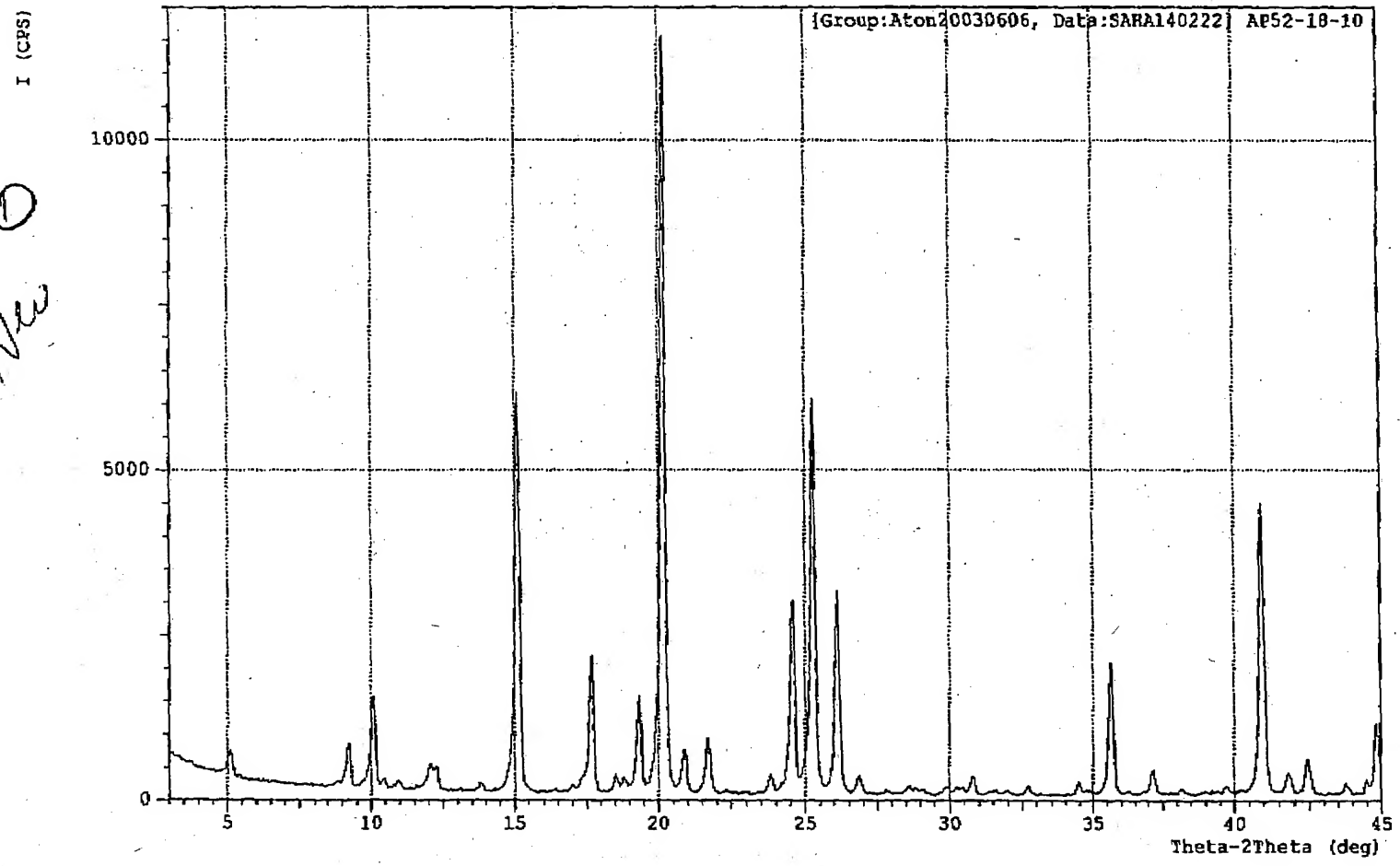
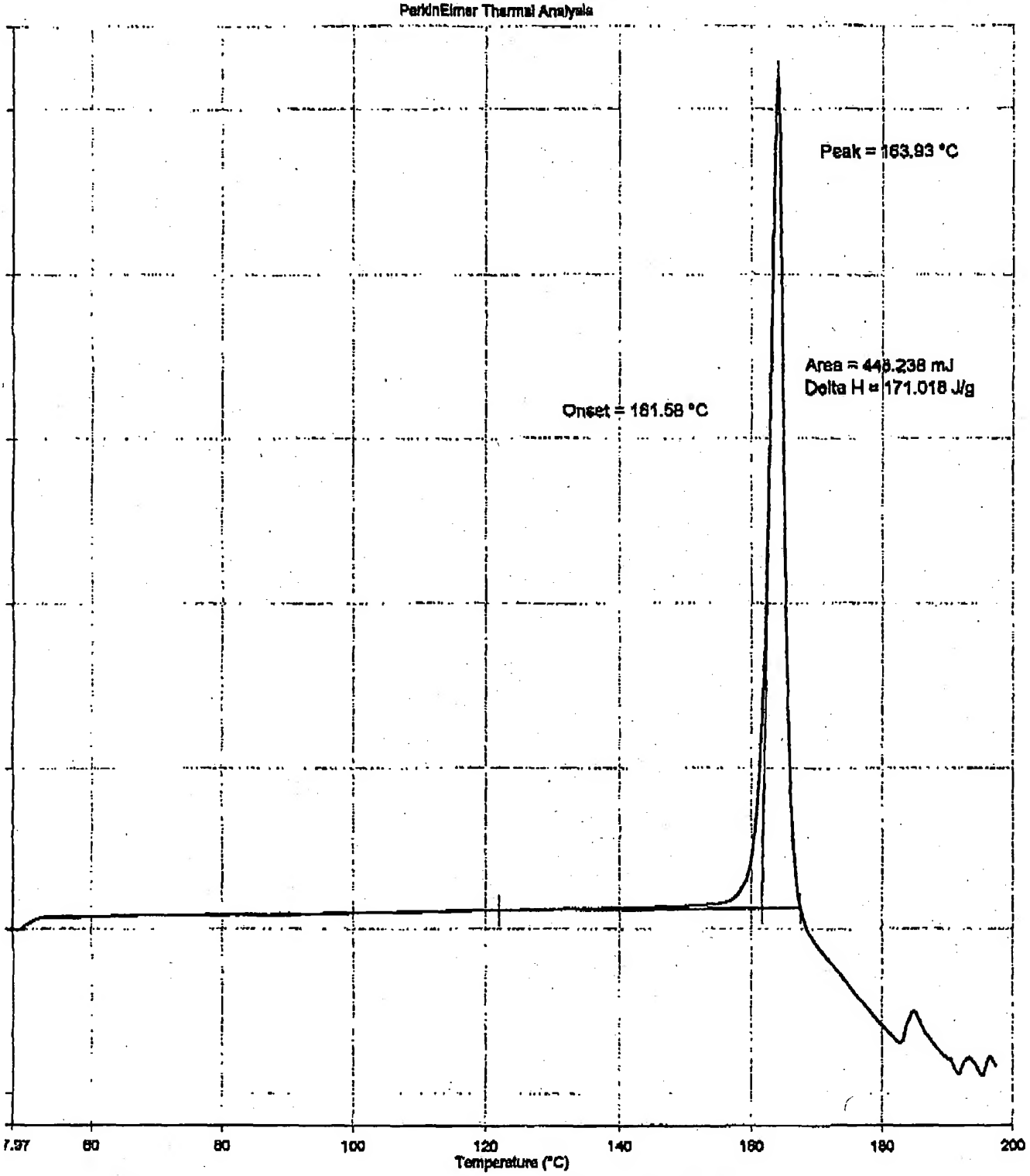


Fig 14A
S Montgomery 12/19/02
Ref SOS-1-94

me: C:\Program Files\Pyris\Data\...\SAHA0NSE12.000
Collected: 12/19/2002 6:54:43 PM
tor ID: Stephanie Monteau
e ID: SAHA 1004C
e Weight: 2.621 mg
Number: 520N5030810
ent: SAHA Onset Method

SM 12/20/02

PerkinElmer Thermal Analysis



id for 1.0 min at 50.00°C
2) Heat from 50.00°C to 200.00°C at 10.00°C/min

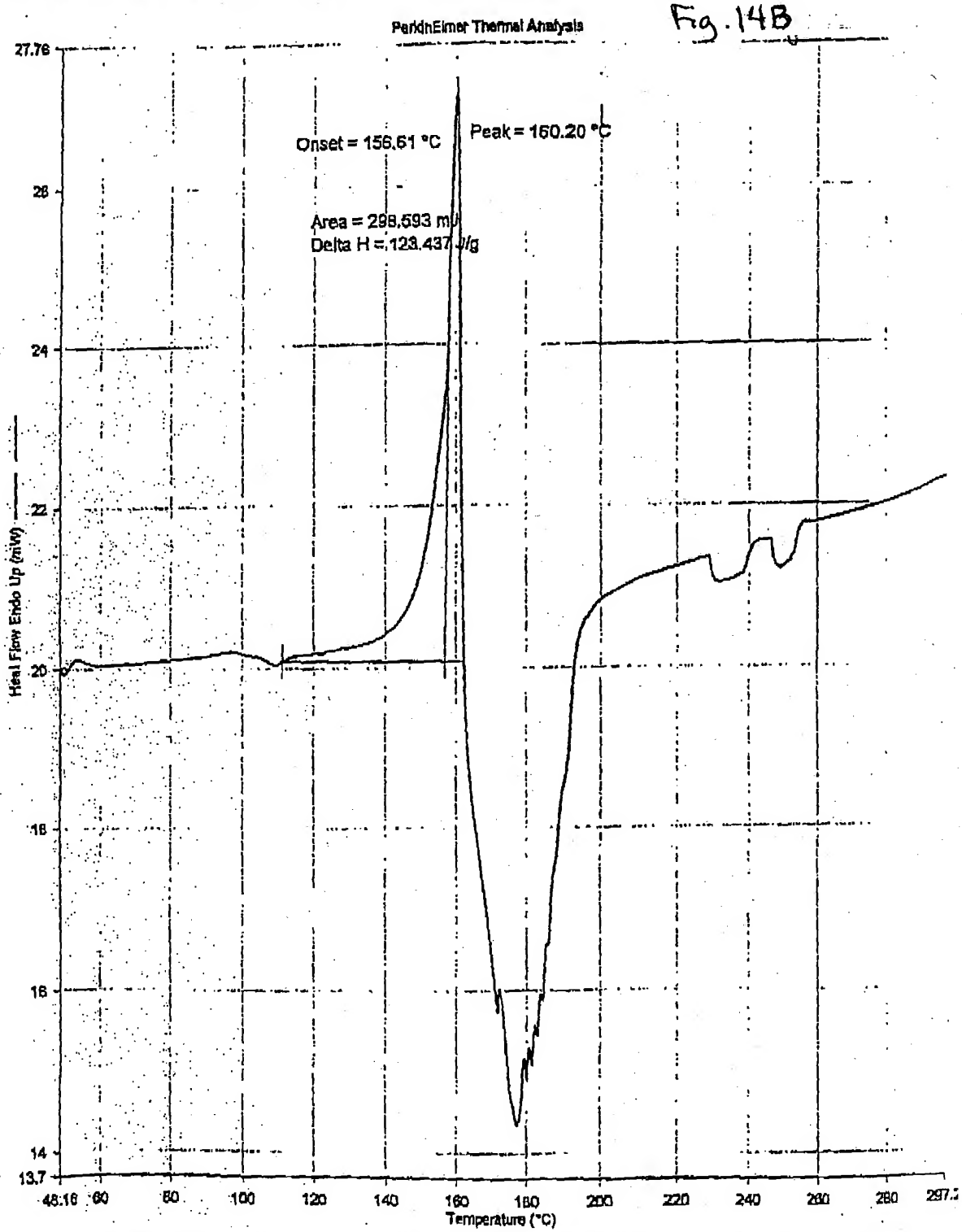
TOTAL P.02

A1

Fig. 14B

Heat Flow Endo Up (mW) : Steps: 1-2

Operator ID: Stephanie Monteau
Sample ID: AP52-14-9-1
Sample Weight: 2.419 mg
Serial Number: 52DNS030810
Comment: SAHA Onset Method



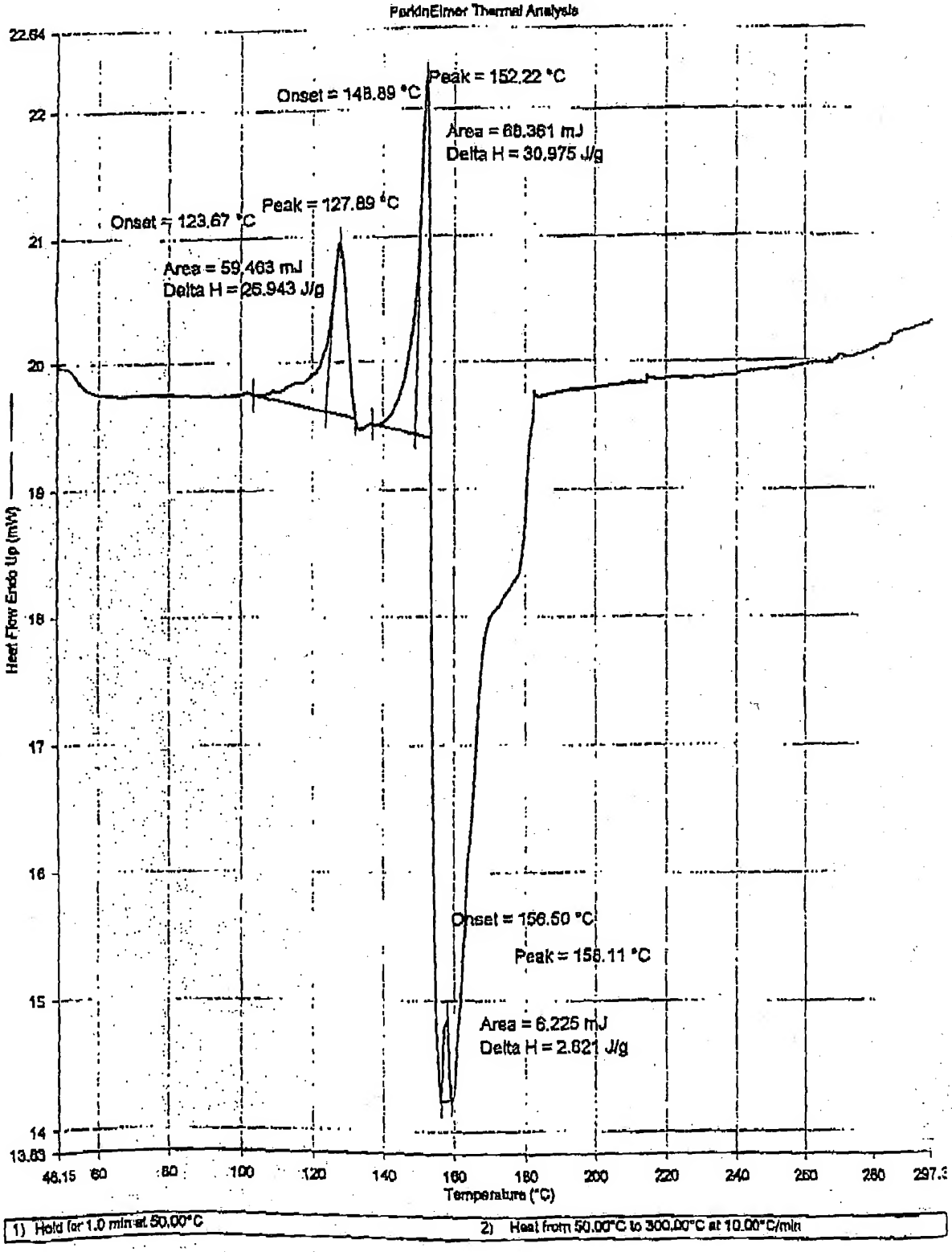
1) Hold for 1.0 min at 50.00°C
2) Heat from 50.00°C to 300.00°C at 10.00°C/min

Data Collected: 5/28/2003 12:18:46 PM
Operator ID: Stephanie Monteau
Sample ID: AP48-43-4
Sample Weight: 2.207 mg
Serial Number: S20N5030810
Comment: SAHA Onset Method

AP48-43-4
Heat Flow Endo Up (mW) : Steps: 1-2

Fig. 14C

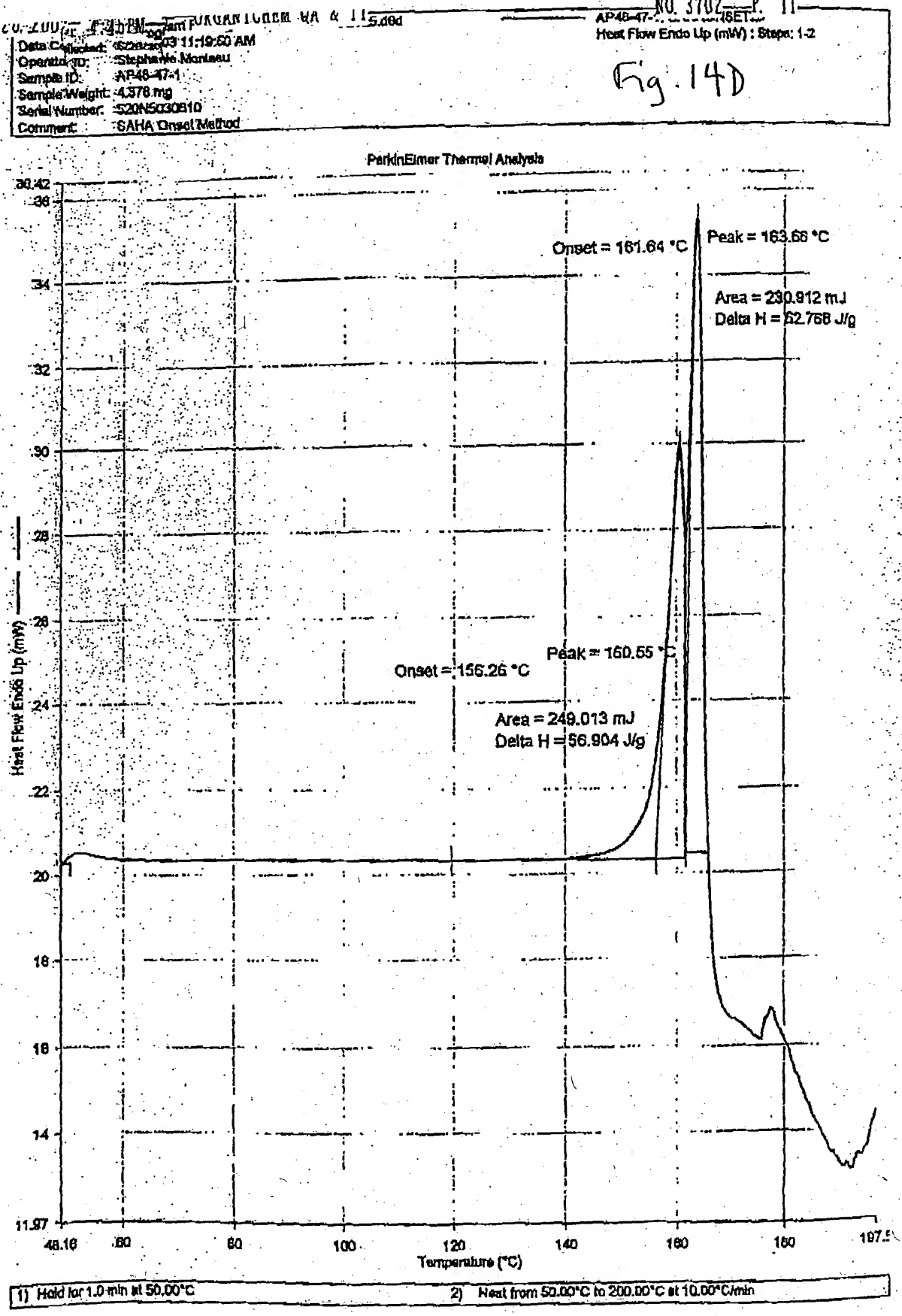
B2



1) Hold for 1.0 min at 50.00°C
2) Heat from 50.00°C to 300.00°C at 10.00°C/min

Fig. 14D

CI


AP48-47-1 SET1
Heat Flow Endo Up (mW) : Steps: 1-2
Data Collected: 5/28/2003 11:19:50 AM
Operator ID: Stephanie Monteau
Sample ID: AP48-47-1
Sample Weight: 4.378 mg
Serial Number: S20N5030810
Comment: SAHA Onset Method
PerkinElmer Thermal Analysis
Onset = 161.64 °C
Peak = 163.68 °C
Area = 230.912 mJ
Delta H = 52.768 J/g
Onset = 156.26 °C
Peak = 160.55 °C
Area = 249.013 mJ
Delta H = 56.904 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
1) Hold for 1.0 min at 50.00°C
2) Heat from 50.00°C to 200.00°C at 10.00°C/min

TOTAL P.10

Heat Flow Endo Up (mW) : Steps: 1-2

Sample ID: APS2-16-10
Sample Weight: 2.924 mg
Serial Number: 520N5030810
Comment: SAHA Onset Method

Fig. 14E

D

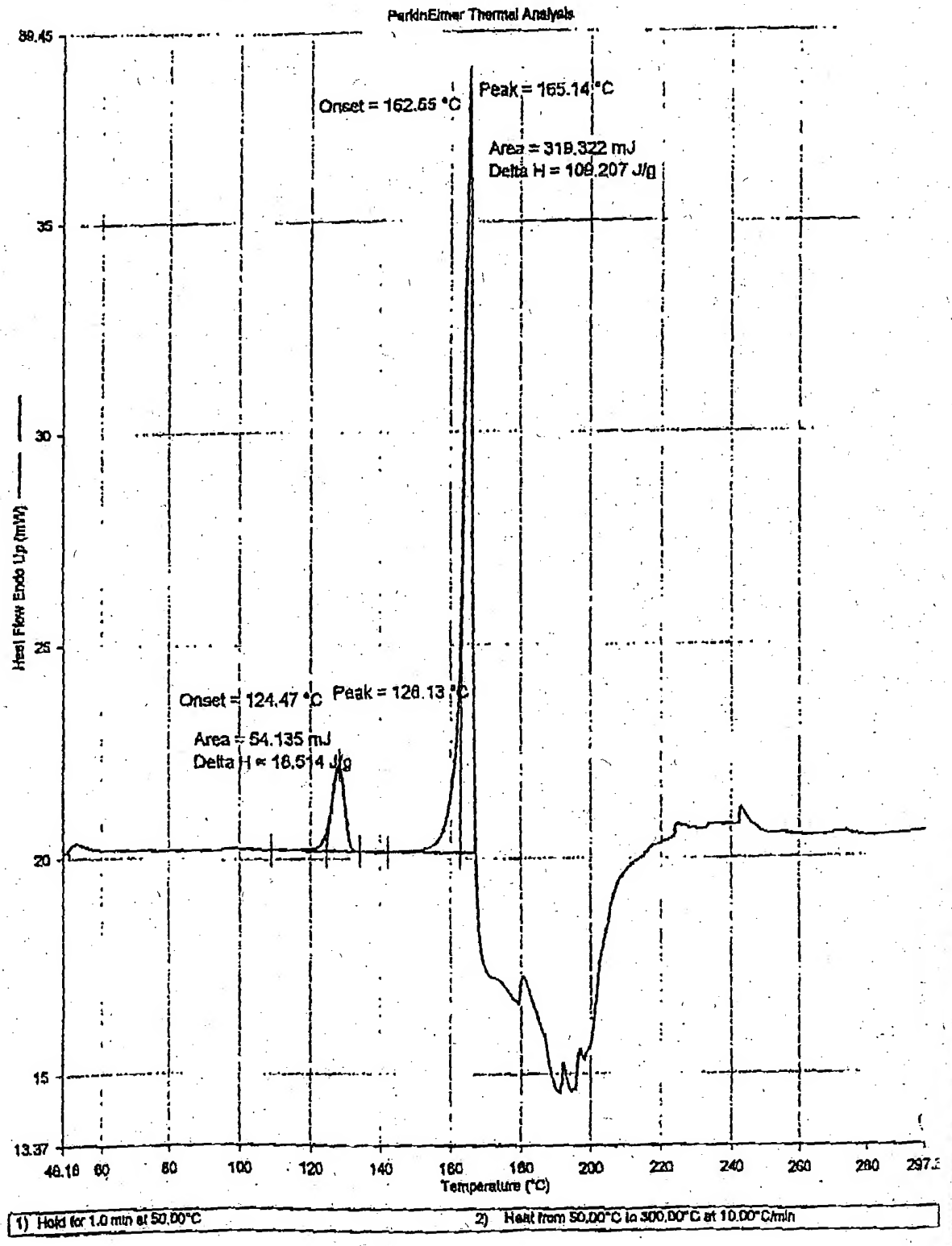


Fig. 15